REMARKS

Amendments

Claims 1-7 and 9-16 have been canceled, claims 8 and 17 and 85 have been amended, and claims 18-23 have been added. Upon entry of the amendment, claims 8 and 17-23 will be pending. Support for the added claims can be found in the specification, for example, in Figures 2A and 2B; Example 1; and in the claims as originally filed.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Specification

The specification had been amended to update cited application information. Previously cited U.S. Patent Application Ser. No. 08/971,310, filed November 17, 1997 (and now abandoned) was converted to 60/084,194, on which issued US patent no. 6,815,185 depends as a priority application filing. Applicant submits that the amendment does not recite new matter as the *only* document incorporated by reference is the disclosure of the originally cited 08/971,310 application. US patent no. 6,815,185 is only being cited as a publicly available document which contains the disclosure of the '310 application.

Rejections

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 8, 10 and 17-25 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility for the reasons of record.

Applicant does not agree. Amended claim 1 is drawn to a transgenic mouse whose genome comprises a disruption in the Cer1 gene, said disruption comprising replacement of nucleotides corresponding to bases 241 through 528 of SEQ ID NO:1 with a Neo cassette.

1. The Utility Requirement

Section 101 of the Patent Act of 1952, 35 U.S.C. § 101, provides that "whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," may obtain a patent on the invention or discovery.

According to the Federal Circuit:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See Brenner v. Manson, 383 U.S. 519, 534, 16 L. Ed. 2d 69, 86 S. Ct. 1033 (1966); Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); Fuller v. Berger, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

(*Juicy Whip v Orange Bang*, 185 F.3d 1364; 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999)(emphasis added)).

2. Well-Established Utility

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

Applicant submits that in light of arguments of record, a person of ordinary skill in the art would immediately appreciate why the invention is useful. Thus, it cannot be reasonably debated that a person of ordinary skill in the art would not immediately appreciate why the invention is useful: for determining gene function. (Applicant notes Examiner's statement that one skilled in the art would have been motivated to make knockout mice to gain clues with regard to gene function (page 19)).

3. Substantial Utility

The Examiner argues that the asserted utilities are not substantial.

According to the MPEP:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. . . . the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;
>
> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

(MPEP § 2107.01 I)(emphasis added).

The MPEP additionally provides:

> Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I).

A use is not substantial where further research is required to identify any use. This is not the case in the present application. Knockout mice have a well-known use in the study of gene function. In the present case, the instant invention does not require further research to establish a utility. Applicant has determined that the CER1 gene is associated with, for example, hypoactivity, fear and anxiety. No further research is required to establish any use. Whether additional research is required to identify therapeutic agents targeting the CER1 gene or to further characterize the function of the CER1 gene is irrelevant to whether the claimed invention has satisfied the utility requirement (see, for example, *In re Brana*, "Usefulness in patent laws . . . necessarily includes the expectation of further research and development.")

In addition, the invention has a "real world use" as demonstrated by: (1) delivery of the claimed invention to at least one large pharmaceutical company (if Examiner requires an affidavit, Applicant shall so provide one); and (2) commercial use of DeltaBase by three of the world's largest pharmaceutical companies, Merck, Pfizer and GlaxoSmithKline. DeltaBase incorporates the data set forth in the specification with regard to phenotypic analyses of the claimed mouse.

In *Raytheon*, the Federal Circuit held:

> A correct finding of infringement of otherwise valid claims mandates as a matter of law a finding of utility under § 101. *See e.g., E.I. du Pont de Nemours & Co. v. Berkley & Co., supra,* 620 F.2d at 1258-61, 205 USPQ at 8-11; *Tapco Products Co. v. Van Mark Products Corp.*, 446 F.2d 420, 428, 170 USPQ 550, 555-56 (6th Cir.), *cert. denied*, 404 U.S. 986, 92 S. Ct. 451, 30 L. Ed. 2d 370 (1971). The rule is not related, as Raytheon argues, to whether a defendant may simultaneously assert non-utility and non-infringement; a defendant may do so. The rule relates to the time of decision not to the time of trial, and is but a *common sense approach to the law*. ***If a party has made, sold, or used a properly claimed device, and has thus infringed, proof of that device's utility is thereby established***. *People rarely, if ever, appropriate useless inventions*.
>
> Proof of such utility is further supported when, as here, the inventions set forth in [the] claims . . . have on their merits been met with commercial success.

Raytheon Co. v. Roper Corp. 724 F. 2d at 959; see also, *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1327, 6 U.S.P.Q.2d 1065 (D. Del. 1987), *affirmed*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989)); *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)(a patent system must be related to the world of commerce rather than to the realm of philosophy).

The Federal Circuit has recently cited *Raytheon* reiterating the position that commercial success may support the utility of an invention. *In re Fisher* at 22, citing *Raytheon Co. v. Roper*, 724 F.2d 951, 220 U.S.P.Q. 592 (Fed. Cir. 1983) (Fisher did not present any evidence showing that agricultural companies have purchased or even expressed any interest in the claimed ESTs. And, it is entirely unclear from the record whether such business entities ever will.) Unlike *Fisher*, Applicant has submitted evidence that the claimed invention has been purchased and delivered to at least one large pharmaceutical company. Unlike *Fisher*, Appellant has presented evidence that the CER1 knockout mouse is actually been used in the real world.

As held by the Federal Circuit, common sense dictates that "[i]f a party has made, sold, or used a properly claimed device, and has thus infringed, proof of that device's utility is thereby established. People rarely, if ever, appropriate useless inventions." *Raytheon Co. at* 959. As people rarely, if ever, appropriate useless inventions, large pharmaceutical companies, rarely if ever, purchase useless inventions.

Applicant respectfully submits that this evidence establishes the utility of the claimed invention.

4. Specific Utility

The Examiner states that the asserted uses are not specific.

According to the MPEP, "specific utility" means "specific" to the subject matter claimed as compared to a "general utility" that would be applicable to the broad class of the invention (MPEP 2107.01). Use of the CER1 -/- and +/- mice to study the function of the CER1 gene and the association of the CER1 gene with, for example, fear, anxiety and hypoactivity, is specific to this mouse. Even if there were many other genes associated with these phenotypes, only the CER1 knockout mouse (as opposed to all other knockout mice) would be used to study the specific role of this gene. The Examiner is respectfully requested to explain (1) how the asserted utility of determining the function of the CER1 gene would be applicable to all other knockout mice; and (2) how the asserted use of studying the association of the CER1 gene with fear, anxiety and hypoactivity would be applicable to all other knockout mice. The Examiner is requested to explain how all other knockout mice would be used to study the function of the CER1 gene.

5. In re Brana

Applicant submits that the legal principles as well as the facts of *Brana* are applicable to the present case. In *Brana*, the Board held that the applicant's specification failed to disclose a specific disease against which the claimed compounds were useful. The Federal Circuit reversed and held that the mouse tumor model represented a specific disease against which the compounds were effective. It is Applicant's position that a mouse demonstrating, for example, decreased average velocity and decreased total distance traveled in the open field test, is sufficient to establish the animal's use as a model for hypoactivity. As in *Brana*, confirmation of

the phenotype in humans is unnecessary. In *Brana*, the PTO was aware of the asserted use against the mouse tumor lines but did not find the use specific – as in the present case:

> Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, see supra note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested in vivo for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, 14 applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in Kirk and Kawai. See, e.g., Cross v. Iizuka, 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in Kirk and Kawai.)
>
> The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

(*Brana* at 1440). The court went on:

> The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.
>
> The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.

> The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.
>
> If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

(*Brana* at 1443-44). The court's position is reflected in the MPEP: if an "assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility" (MPEP § 2107, II (A)(3); II (B)(1)). If it is well known to those skilled in the art that knockout mice are useful for studying gene function, then those skilled in the art would certainly regard such use as credible, specific and substantial. Nothing more is required to satisfy the statutory requirement. Applicant submits that, as in *Brana*, one skilled in the art would find the asserted use credible, substantial and specific.

6. Additional Examiner Arguments

The Examiner questions the validity of the tests used to evaluate behavior.

The disclosed tests are standard in the art. The results and conclusions would be acceptable to one skilled in the art. For example, with regard to fear and anxiety, Crawley states:

> The earliest quantitative measures of fear-related behavior in mice were freezing and defecation in a brightly lit open field environment.

(What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000)(page 183)(copy of relevant pages attached).

With regard to hypoactivity, Crawley states:

> The most standardized general measure of motor function is spontaneous activity in the open field. . . .
> A 5-minute test session in a novel open field is sufficient to detect highly significant hyperactivity or behavioral sedation.

(pages 48, 50).

With regard to depression, Crawley states:

> The tail suspension test has some of the characteristics of the Porsolt swim test and has been successfully used for mice in several laboratories.

(page 194).

The Examiner again argues that the phenotype of a knockout mouse could result from compensation by other proteins in the same pathway, citing Olsen in support of this position.

Applicant disagrees. First, whether the phenotype is a direct or indirect result of the null allele does not affect the utility of the mouse to determine the function of the gene, and is irrelevant to whether the claimed invention satisfies the utility requirement. The phenotypes of the claimed mice reveal that Cerl plays a role in hypoactivity, fear and anxiety. The null Cerl mouse clearly is useful in elucidating the role Cerl plays in these processes.

Further, Olsen's comments regarding compensation relate to the case when a knockout results in lethality or more particularly when there is no apparent phenotype. Such is not the case here. Applicant has demonstrated that the null Cerl allele results in very specific phenotypes. Olsen does not provide any evidence that the phenotype has been determined to result from compensation by another protein in the same pathway, as suggested by the Examiner.

In fact, Olsen supports Applicant's position that knockout mice are useful in determining the function of a target gene. Olsen describes knockout mice with null disruptions in several different subtypes of GABA receptors or related proteins. In each case, even with unexpected, lethal or a lack of phenotype, the mice revealed some role or function for the receptor subtype. Clearly, the knockout mice described were useful in determining the function of the GABA receptor.

In the conclusion, Olsen states "the use of mutant and knockout mice has aided understanding of the roles of GAD and GABAR in the intact mammalian organism, with much promise for additional information to come." (page 91). Even with respect to mice having increased lethality, Olsen states: "[t]he γ2 and β3 subunit knockouts are associated with early postnatal lethality but have nonetheless provided considerable new information about their importance, including relevance to neurodevelopment, synaptogenesis, and possibly human disease. The β3 is a strong candidate for involvement in the epilepsy and other phenotypic attributes of Angelman syndrome, a human genetic disorder characterized by mental retardation, seizures, motor incoordination, and sleep disturbances. The γ2L knockout has allowed direct testing and negation of the selective subunit hypothesis for ethanol modulation of GABAR function. The δ subunit knockout appears to provide information about the function of GABAR in adult cerebellum, dentate gyrus of the hippocampal formation, and the thalamus. GAD_{65},

GABAR β3, and GABAR δ subunit knockouts all exhibit spontaneous seizures, but of different sorts, confirming suspicions that GABAR malfunction might produce epilepsy by more than one mechanism and providing excellent animal models for investigation of the cause of the seizure phenotype." (page 91-92).

Olsen goes further: "[i]n summary, transgenic and knockout mice have demonstrated that GABA plays a major role in brain development, control of palate formation, and epileptogenesis via multiple mechanisms." (page 92). It is untenable to cite Olsen as standing for the proposition that knockout mice do not have a well-accepted use in determining gene function.

With regard to Austin and the NIH citation, the Examiner argues that the references were published well after the present application was filed.

The Examiner cites no legal support why Austin and NIH references should not be considered. The references are not being cited to support a post-filing assertion of utility. The goal of determining gene function is clearly set forth in the specification. Austin supports this statement. Moreover, courts have accepted post-filing activities to support an asserted utility. For example, in *In re Brana*, the application's filing date was June 30, 1988. The applicants relied on an affidavit submitted June 19, 1991 to provide evidence of the compounds activity, *a date well after the filing date*. The Federal Circuit noted:

> Enablement, or utility, is determined as of the application filing date [citations omitted]. The Kluge declaration, though dated after applicants filing date, can be used to substantiate any doubts as the asserted utility since this pertains to the accuracy of a statement already in the specification. [citations omitted] It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (*i.e., demonstrated utility*).

(*Brana*, n.19). Thus, Austin and the NIH citation should have been considered by the Examiner as evidence supporting the utility of the claimed invention.

As noted by the Examiner, Austin states knockout mice "can" be used to elucidate gene function. Therefore, the asserted use is credible.

The Examiner argues that the observed phenotype "may" not be the result of the disruption itself.

The Examiner's argument is based on conjecture. Scarff remarks that retention of a selectable marker "*can* lead" to "confounding phenotypes." There is no evidence that the Neo cassette is causing "confounding" phenotypes in the presently claimed invention. Moreover, it is

unreasonable to expect the patentee to exclude this *possibility*. As argued above, Applicant has credibly set forth data showing that Cerl -/- mice possess phenotypes not observed in Cerl +/+ mice. One skilled in the art would accept that such findings indicate that the phenotypes are associated with the function of the Cerl gene.

The Examiner states that Scarff cites Fiering, Hug, Pham, Leder, DeJarnette and Ren.

The Examiner has not stated what any of these references disclose nor has the Examiner provided copies of any of these references. Applicant is unable to comment on their content.

7. Summary

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying Cerl gene function with respect to the cited phenotypes, for studying gene expression, and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly made a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant to be specific and substantial. (*In re Brana*; MPEP § 2107).

Rejection under 35 U.S.C. § 112, first paragraph

Claims 8, 10, and 17-25 are rejected because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility for the reasons set forth in the utility rejection. Applicants respectfully traverse the rejection. For the reasons set forth above, the claimed invention satisfies the utility requirement. Therefore, one skilled in the art would know how to use the invention.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 8, 10 and 17-25 stand rejected as allegedly failing to comply with the written description requirement.

The Examiner argues that "null allele" is new matter.

The claim has been amended, without prejudice.

Withdrawal is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 8, 10 and 17-25 have been rejected as being indefinite.

The Examiner argues that "null cerberus allele" is indefinite.

Applicant does not agree. However, the claims have been amended without prejudice to reflect a disruption in the Cerl gene.

Claim 10 has been canceled rendering the rejection moot.

Withdrawal is respectfully requested.

Rejection under 35 U.S.C. § 102(a)

Claims 8, 10 and 17-24 stand rejected as being anticipated by Stanley.

Stanley discloses a mouse having the first coding exon of the *Cerl* gene replaced with a *lacZ* reporter. According to an NCBI web search, Stanley was in April 2000.

The present invention was reduced to practice prior to the publication of the Stanley reference. Applicant submits herewith a declaration from Michael Leviten, a co-inventor of the claimed invention. As Stanley is not prior art, the reference does not anticipate the claimed invention. Withdrawal is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 8, 10 and 17-25 stand rejected as being obvious over Conquet in view of Mara. Conquet is disclosed as showing heterozygous and homozygous mice having a lacZ insert. Mara is cited as teaching SEQ ID NO: 1. The Examiner argues that the phenotypes recited in claims 17 and 20 are inherent to the mice taught by Conquet and Mara.

First, inherency is relevant to an inquiry under section 102 for anticipation, not for obviousness under section 103. (See MPEP 2141.02. Obviousness cannot be predicated on what

is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert* 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993)).

Second, as a preliminary matter, Applicant questions how the Examiner can argue that the requisite motivation exists to create the claimed invention, when the Examiner argues above that the claimed invention has no patentable utility and that one skilled in the art would not know how to use the invention.

A proper analysis under section 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition; and (2) whether the prior art would also have revealed that in so making, those of ordinary skill would have a reasonable expectation of success (*In re Vaeck* 20 USPQ2d 1438 (Fed. Cir. 1991).

Neither factor is satisfied here. The cited references, neither alone or in combination, teach or suggest the presently claimed invention. The Examiner has not cited any evidence in the references that this gene be disrupted.

In addition, the cited references fail to teach or suggest each claim limitation. The claimed invention is drawn to a transgenic mouse whose genome comprises a disruption in the Cer1 gene, said disruption comprising replacement of nucleotides corresponding to bases 241 through 528 of SEQ ID NO:1 with a Neo cassette. There is no teaching or suggestion of a transgenic mouse whose genome comprises a disruption of the endogenous Cer1 gene. Moreover, there is no teaching of the specifically recited disruption. As the claimed invention would not have been obvious, withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks, Applicant respectfully requests reconsideration and a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **502775**.

Respectfully submitted,

11-22-05
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